Thyrotoxic periodic paralysis

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Thyrotoxic periodic paralysis (TPP), a disorder most commonly seen in Asian men, is characterized by abrupt onset of hypokalemia and paralysis. The condition primarily affects the lower extremities and is secondary to thyrotoxicosis. It has been increasingly reported in the USA due to the rise in the immigrant population. Hypokalemia in TPP results from an intracellular shift of potassium induced by the thyroid hormone sensitization of Na^+/K^+–ATPase rather than depletion of total body potassium. Treatment of TPP includes prevention of this shift of potassium by using nonselective beta-blockade, correcting the underlying hyperthyroid state, and replacing potassium. TPP is curable once a euthyroid state is achieved. It is important for physicians to distinguish TPP from familial hypokalemic periodic paralysis, a more common cause of periodic paralysis in Caucasians. The absence of a family history of paralysis, male sex, presentation in the second to fourth decades of life, and signs of thyrotoxicosis like sinus tachycardia help in the diagnosis of this disorder. Early recognition of TPP is vital to initiating appropriate treatment and to avoiding the risk of rebound hyperkalemia that may occur if high-dose potassium replacement is given.

Thyrotoxic periodic paralysis (TPP) is most common in Asian populations, with an incidence of approximately 2% in patients with thyrotoxicosis of any cause. It has been recognized in Thais, Filipinos, Vietnamese, Koreans, Malaysians, Hispanics, African Americans, and Caucasians (1–5). TPP is characterized by acute onset of severe hypokalemia and profound proximal muscle weakness in patients with thyrotoxicosis (1).

TPP is commonly misdiagnosed in western countries because of its similarities to familial periodic paralysis. Familial periodic paralysis is an autosomal dominant disorder caused by a defect in the gene coding for L-type calcium channel 1-subunit *(CACNA1S)* on chromosome 1q31–32 (2). The neuromuscular presentations of both are identical, and to enhance diagnosis of TPP, physicians need to look for subtle features of hyperthyroidism in the presence of hypokalemic periodic paralysis. Early diagnosis not only aids in definitive management with nonselective beta-blockers and correction of hyperthyroidism, but also prevents the risk of rebound hyperkalemia due to excessive potassium replacement.

CASE REPORT

A 33-year-old Hispanic man with a history of recurrent hypokalemia and muscle weakness presented to our emergency department with generalized muscle weakness more pronounced in his lower extremity. The patient's symptoms started in the early morning, and he was unable to walk to the bathroom. He had had similar episodes before and took potassium supplements sporadically. His initial episode of hypokalemia and paralysis had occurred 2 years earlier. He denied use of diuretics, laxatives, alcohol, or recreational drugs. He reported intermittent palpitations and diarrhea and had no family history of periodic paralysis.

On physical examination, he had a mildly enlarged thyroid with firm consistency, an irregular heart rate, and decreased muscle strength and tendon reflexes in both lower extremities. He had no exophthalmos or sensory or cranial nerve deficits.

In the emergency department, his initial potassium level was 1.7 mEq/L (reference range, 3.6–5.0 mEq/L) with normal acid-base status. His serum phosphorus level was 4.0 mg/dL (reference range, 2.7–4.5 mg/dL), and his serum magnesium level was 1.4 mg/dL (reference range, 1.7–2.6 mg/dL) on admission. Urine potassium per 24 hours was 83 mmol/day (reference range, 25–125 mmol/day), and an electrocardiogram showed atrial fibrillation with a ventricular rate of 90 beats per minute. An initial diagnosis of periodic hypokalemic paralysis was made. He was given 40 mEq of intravenous potassium chloride in the emergency department and was then started on a normal saline infusion with 20 mEq/L of potassium. He was also placed on an oral potassium replacement protocol, which resulted in resolution of his lower-extremity paralysis.

On the second day of admission, his serum potassium level increased to 4.8 mEq/L; serum phosphorus, to 4.2 mg/dL; and serum magnesium, to 1.6 mg/dL. The results of a computed tomography scan of his abdomen were normal, and his renin

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and aldosterone levels were within normal limits. Atrial fibrillation persisted even after correction of his hypokalemia, and thyroid function tests were ordered. The thyroid-stimulating hormone level was <0.02 mU/L (reference range, 0.50–6.80 mU/L), and the free thyroxine (T_4) level was 4.56 ng/dL (reference range, 0.89–1.76 ng/dL). Thyrotoxicosis was diagnosed, and the patient was given propranolol 10 mg three times a day. The dose was quickly increased to 40 mg three times a day. The patient's thyroid-stimulating immunoglobulin level was elevated, and he was started on methimazole 20 mg per day. His thyroid uptake scan was pending at the time of discharge, as he had received iodine contrast for his abdominal computed tomography scan. Serial measurements of his serum potassium level in the hospital remained within normal limits without oral potassium supplements. The patient was discharged home with the diagnosis of TPP secondary to Graves' disease.

DISCUSSION

Even though it is commonly seen in Graves' disease, TPP is not related to the etiology, severity, and duration of thyrotoxicosis (1). Family history of periodic paralysis is usually absent, although the presence of different HLA antigen subtypes such as DRw8, A2, Bw22, Aw19, B17, B5, and Bw46 in certain ethnic populations may make them more susceptible to TPP (6, 7).

Pathophysiology

The pathogenesis of hypokalemic periodic paralysis in certain populations with thyrotoxicosis is unclear. Transcellular distribution of potassium is maintained by the Na^+/K^+–ATPase activity in the cell membrane, and it is mainly influenced by the action of insulin and beta-adrenergic catecholamines (8). Hypokalemia in TPP results from an intracellular shift of potassium and not total body depletion. It has been shown that the Na^+/K^+–ATPase activity in platelets and muscles is significantly higher in patients with TPP (9). Hyperthyroidism may result in a hyperadrenergic state, which may lead to the activation of the Na^+/K^+–ATPase pump and result in cellular uptake of potassium (7, 8, 10).

Thyroid hormones may also directly stimulate Na^+/K^+–ATPase activity and increase the number and sensitivity of beta receptors (8, 11). Patients with TPP have been found to have hyperinsulinemia during episodes of paralysis. This may explain the attacks after high-carbohydrate meals (12).

Clinical manifestations

While thyrotoxicosis commonly affects women, TPP is predominantly seen in men in the second to fourth decades of life *(Table 1)*. Patients present with acute onset of proximal symmetrical ascending lower-extremity muscle weakness during the early morning hours or while resting after strenuous exertion and a high-carbohydrate meal. Acute episodes may be preceded by muscle aches, cramps, and muscle stiffness (1–5). Other precipitating factors include trauma, exposure to cold, emotional stress, infection, alcohol ingestion, menses, and drugs like diuretics, insulin, or steroids (5). The paralysis can last 3 to 96 hours, and it resolves in the reverse order from which it occurred. Deep tendon reflexes are decreased or absent (1, 3–5). Rarely does the paralysis affect ocular, bulbar, or respiratory muscles, but ventilatory impairment has been reported (13). Sensation and level of consciousness are usually spared. Findings of thyrotoxicosis such as warm and moist skin, fever, tachycardia, exophthalmoses, or goiter may be subtle but are important clues to the diagnosis. Serious associated morbidities include dysrhythmias, respiratory failure, and death.

Table 1. Clinical manifestations of thyrotoxic periodic paralysis*

General:
Male predominance; initiation at age 20 to 40
Periodic flaccid paralysis of proximal muscles, mainly of lower extremities
Negative family history of similar symptoms
Hypertension
Subtle clinical features of hyperthyroidism
Laboratory findings:
Hypokalemia, hypophosphatemia, and mild hypomagnesemia
Normal acid-base balance
Low potassium excretion rate (low urinary potassium–creatinine ratio and low TTKG)
Hypercalciuria and hypophosphaturia
Abnormal thyroid function tests (low TSH; elevated free and total T_4 and T_3; increased T_3 uptake)
Electrocardiographic abnormalities:
Sinus tachycardia
Hypokalemic changes: prominent U wave, prolonged PR interval, increased P-wave amplitude, widened QRS complexes
First-degree atrioventricular block
Atrial and ventricular arrhythmias

*Adapted from references 1, 3, 7, and 14.

TTKG indicates transtubular potassium gradient (a semiquantitative index of the activity of the potassium secretory process calculated as [urine K ÷ (urine osmolality/plasma osmolality)] ÷ plasma K); TSH, thyroid-stimulating hormone; T_4, serum thyroxine; T_3, triiodothyronine.

Management

Periodic paralysis can manifest with any condition associated with hypokalemia *(Table 2)*. The initial diagnostic approach begins with a detailed clinical history, physical examination, assessment of acid-base status, and a spot test of urine electrolytes for potassium excretion (ratio of urine potassium to urine creatinine) (8). The urine potassium–creatinine ratio and transtubular potassium gradient (TTKG) are useful indices to diagnose hypokalemia secondary to renal loss. The TTKG is a semiquantitative index of the activity of the potassium secretory process, calculated as [urine K ÷ (urine osmolality/plasma osmolality)] ÷ plasma K. Normal acid-base status and low urinary potassium excretion (urine potassium–creatinine ratio <2 and TTKG <3) are characteristics of hypokalemia in TPP (7, 14–16). Transient hypophosphatemia and hypomagnesemia have been documented along with elevation in creatine phosphokinase in patients with TPP. These disturbances correct as the acute thyrotoxicosis resolves (3). The serum thyroid-

Table 2. Differential diagnosis of hypokalemic paralysis*

Type of potassium imbalance	Cause
Transcellular shift	Drugs (tocolytics, theophylline toxicity, chloroquine toxicity, insulin overdose)
	Thyrotoxic periodic paralysis
	Familial periodic paralysis
	Sporadic periodic paralysis
	Barium poisoning
Renal loss of potassium	Drugs: diuretics
	Primary hyperaldosteronism
	Pseudohyperaldosteronism: licorice ingestion
	Bartter's syndrome, Gitelman's syndrome
	Renal tubular acidosis
	Other: nephrotic syndrome, acute tubular necrosis, diabetic ketoacidosis, and ureterosigmoidostomy
Gastrointestinal loss of potassium	Celiac disease
	Tropical sprue
	Infectious diarrhea: *Salmonella* enteritis, *Strongyloides* enteritis, and *Yersinia* enterocolitis
	Short bowel syndrome

*Adapted from references 2, 7, 8, 14, and 19.

stimulating hormone level is low, and free thyroxine (free T_4), triiodothyronine resin uptake, and total triiodothyronine levels are elevated. Electrocardiographic findings may be characteristic of hypokalemia, with increased P-wave amplitude, prolonged PR interval, widened QRS complexes, decreased T-wave amplitude, and U waves. Unlike hypokalemia from other causes, sinus tachycardia predominates in patients with TPP (17, 18). Other electrocardiographic abnormalities include atrioventricular block, atrial fibrillation, ventricular fibrillation, and asystole (19).

Management of TPP includes correction of hypokalemia and treatment of the underlying hyperthyroid state. Traditionally, patients are given intravenous or oral potassium to hasten muscle recovery and prevent cardiopulmonary complications; however, there is a danger of rebound hyperkalemia due to release of potassium and phosphate from the cells on recovery (3, 19). Rebound hyperkalemia occurred in approximately 40% of patients with TPP, especially if they received >90 mEq of potassium chloride within the first 24 hours (3). There is a positive correlation between the dose of potassium chloride administered and the degree of rebound hyperkalemia (3, 19, 20). Patients receiving a total dose of ≤50 mEq of potassium chloride rarely develop rebound hyperkalemia. Lower doses of potassium chloride may be effective while lowering the patient's risk of hyperkalemia (20).

In the setting of TPP, propranolol, a nonselective beta-blocker, prevents the intracellular shift of potassium and phosphate by blunting the hyperadrenergic stimulation of Na^+/K^+–ATPase (21). It has been observed that propranolol given alone either orally (3 mg/kg) or intravenously normalizes serum potassium levels on an average of 120 minutes; hence, initial therapy for stable TPP should include propranolol (19, 22–25). The combination of nonselective beta-blockers and low-dose potassium appears to be the treatment of choice for facilitating recovery and reducing rebound hyperkalemia. The definitive therapy for TPP includes treatment of hyperthyroidism with antithyroid medications, surgical thyroidectomy, or radioiodine therapy. After initiation of definitive therapy, patients should avoid precipitating factors and continue propranolol until a euthyroid state is achieved to prevent recurrence (7, 20, 21). TPP is curable once a euthyroid state is achieved.

CONCLUSION

The events that lead to paralysis in patients with TPP are complex. They include hyperthyroidism, a genetic/racial predisposition, an exaggerated insulin response, and a hyperadrenergic state. Diagnosis of TPP at the initial encounter is often delayed and confused with more familiar causes of hypokalemia and lower-extremity paralysis, partially because of the subtleness of the thyrotoxicosis and partially because of unawareness about this disorder (3). TPP has been increasingly documented in Asian and Hispanic populations in the USA, and physicians may encounter this disorder more frequently. Treatment with low-dose potassium supplements and nonselective beta-blockers should be initiated upon diagnosis, and the serum potassium level should be frequently monitored to prevent rebound hyperkalemia. Increased awareness among physicians about this disorder will result in early diagnosis, appropriate treatment, and the prevention of rebound hyperkalemia.

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